Papers and Originals

Changing Tides of Chemotherapy of Malaria

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> "What's done we partly may compute,
> But know not what's resisted."—Robert Burns.

From the time of Ehrlich's great discoveries the progress of the treatment of protozoan infections was repeatedly impeded by the appearance of drug resistance due to the modified response of the parasite to the chemical compound that originally showed much promise. Findlay (1950) referred to the alternation of light and darkness, of growth and rest, in the history of chemotherapy and forecast the difficulties bound to arise because of the "increasing dominance of drug-fast parasites" which "may equal or even defeat the ingenuity of man."

Synthetic Antimalarials

After three centuries of reliance on cinchona bark and quinine the development of synthetic antimalarials was initiated by German scientists, leading in 1926 to the discovery of pamaquin ("plasmoquine"). Within five years from that date rhodoquine (Fourneau 710) was synthesized by the French and mepacrine ("atebrine") by the Germans. The outstanding role of mepacrine (atebrine, "quinacrine," "acriquine," etc.) for prevention and treatment of malaria in all the armed Forces during the period 1940–5 belongs to medical history and was described by Findlay (1951) and by Russell (1955). In Australia the magnificent work of Fairley (1949), who assessed in a way never before attempted the value of antimalarial drugs on nearly one thousand Army volunteers infected with malaria, marked a new era in research.

The discovery in the United Kingdom in 1944 of proguanil—an entirely new and remarkable antimalarial compound—was another milestone in the history of modern chemotherapy, though this drug came too late to play its full part in the prevention of malaria during the last war (Davey, 1955).

The value of 4-aminoquinoline compounds, developed in the 1930s by the Germans, was recognized only ten years later, when the French began to use some of them in North Africa (Schneider *et al.*, 1948). A remarkably co-ordinated programme, instituted in the U.S.A. in 1941, screened within four years over 16,000 compounds, of which 80 were selected for testing in human malaria (Coatney *et al.*, 1952). The fascinating story of the initial discovery of chloroquine, of its erroneous rejection, rediscovery, evaluation, and final acceptance as the most valuable antimalarial has been told by Coatney (1963). Amodiaquine—another 4-aminoquinoline derivative—was found to be just as effective, and among a number of 8-aminoquinoline compounds primaquine was thought to be the best for radical cure of relapsing malaria. Quinocide, a drug closely allied to primaquine, was studied and widely used in the U.S.S.R.

It has been pointed out by Covell *et al.* (1955) that no serious problems arose when we had only three main antimalarials: quinine, pamaquin, and mepacrine. However, within a few years after the large-scale use of proguanil, reports of experimentally produced resistance in animal parasites were followed during the period 1947–53 by a series of observations of drug-resistance of human plasmodia from Malaya, Indonesia, New Guinea, Assam, and later (to chlorproguanil—a closely related compound) from Ghana.

The same events occurred with regard to the next remarkable drug of the "antifolic acid" category—namely, pyrimethamine, developed in 1950 jointly by the Americans and the British (Schnitzer and Grunberg, 1957; Bishop, 1959; Schnitzer and Hawking, 1963).

First field reports on pyrimethamine resistance of *Plasmodium falciparum* and *P. malariae* in man came from Kenya (Jones, 1954, 1958) and from Tanganyika (Clyde and Shute, 1954). There followed reports on pyrimethamine resistance in the Cameroons, the Volta Republic, Northern Nigeria, South-Western Nigeria, and Ghana. Outside tropical Africa pyrimethamine resistance was reported in *P. falciparum* and *P. vivax* from Venezuela, from West New Guinea (West Irian), and from Cambodia (W.H.O., 1961). In the course of experimental studies Young (1957) and Young and Burgess (1959) reported pyrimethamine resistance in *P. malariae* and *P. vivax* infections in neurosyphilitic patients.

The concept of malaria eradication, which has been developing in Europe and the Americas since the early 'fifties, when the residual insecticides were introduced in many fields of public health, was accepted by the World Health Organization and given an integrated plan in 1956 (W.H.O., 1957). At that time the increasing frequency of reports on resistance of human plasmodia to proguanil and pyrimethamine created some concern and disappointment among the clinicians, but the importance of this phenomenon from the point of view of malaria eradication was relatively small. Firstly, because during the period of the change of strategy from malaria control to malaria eradication the role of drugs was not fully appreciated. Secondly, because it was soon recognized that proguanil and pyrimethamine, particularly valuable for the prevention of infection and for their sporontocidal effect, are rather slow and uncertain therapeutic agents.

Reappraisal

However, the role of chemotherapy in malaria eradication has been reappraised during the past few years; the value of 4-aminoquinolines (chloroquine and amodiaquine) in all phases of the programme has been fully recognized, and the use of these drugs alone or in combination with 8-aminoquinolines has shown over the past three years a continuous upward trend (W.H.O., 1961, 1962).

Antimalarials may be divided into two groups according to their mode of action, and this classification is also due to

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the fact that the sulphonamide-proguanil-pyrimethamine group induces drug resistance fairly easily, while resistance to the quinoline-acridine group seldom occurs (Schnitzer, 1962 ; J. Hill, 1963).

On the basis of previous experimental work and field observations it was believed that in human plasmodia the development of resistance to 4-aminoquinolines was unlikely (Wilson and Edeson, 1958), to say the least. This complacency was shaken when the failure of a standard chloroquine treatment (1,500 mg. of base over three days) to cure a *P. falciparum* infection originating in Colombia was reported by American workers (Moore and Lanier, 1961 ; Young and Moore, 1961 ; Young, 1961, 1962 ; Powell *et al.*, 1963a). The infection was transmitted to neurosyphilitic patients, and this strain responded poorly to several drugs ; it was rapidly cured by quinine. Later, *P. falciparum* infections not responding to the usual curative doses of chloroquine were described in Brazil (Rodrigues, 1961 ; Box *et al.*, 1963).

Reports on apparent chloroquine resistance came recently from Thailand (Harinasuta *et al.*, 1962) and from Malaya (Sandosham, 1963 ; Sandosham *et al.*, 1963 ; Eyles *et al.*, 1963) where infections with *P. falciparum* responded poorly to the usual curative dosage of the drug. In 1962 a strain of *P. falciparum* from Thailand was studied on human volunteers by two independent American teams (Young *et al.*, 1963 ; Powell *et al.*, 1964). A number of cases of malaria in the armed Services in Malaya have occurred during the past two years in spite of the allegedly good discipline of prophylactic proguanil, and some of these infections showed a disappointing response to repeated treatment with chloroquine at usual doses (Montgomery and Eyles, 1964). Powell *et al.* (1963b) reported a chloroquine-resistant strain of *P. falciparum* from South Vietnam. The situation was reviewed by the Malaria Advisory Board of the Federation of Malaya (1963) and a field investigation was set up jointly by the Government of Malaya, the U.S. Public Health Service, and the World Health Organization.

It should be stressed here that, while many observations are reliable, not all reports coming from the field and claiming the presence of chloroquine resistance are of equal value. There is little doubt that some such statements are hasty and may have overlooked the simple fact that the drug was not given or not swallowed, or was vomited, or that the dosage was too low. It seems that "chloroquine resistance" has the appeal of novelty, and it is not easy to distinguish between a genuine drug-fastness and spurious claims caused by poor supervision of drug administration and/or blood examination.

The potential seriousness of the situation created by the possibility of widespread resistance of *P. falciparum* to chloroquine—the most widely used drug in chemotherapy of malaria and a powerful weapon in the service of malaria eradication—was fully recognized by the World Health Organization. Steps were taken to assist any research work in this field and to maintain a close watch on the situation. Particular attention is being paid to careful appraisal of any reports on alleged drug-resistance and to preparation of criteria for the recognition of this phenomenon. A technical meeting convened by the World Health Organization concluded that "confirmation of drug resistance can best be provided through the transfer of the relevant parasite strain to a research centre for investigation on subjects not exposed to reinfection and for the study of the response of the parasite strain to other drugs and its transmission through a mosquito vector" (W.H.O., 1961).

While most of the pioneering work on the dynamics of drug resistance of animal plasmodia has been done in the United Kingdom and in India, the paramount role in the study of drug-resistance in human malaria is now being played by several research institutions in the United States of America, where the suspected drug-fast strains of malaria parasites from tropical areas can be transmitted to non-immune volunteers. Much field-work on the checking of the evidence of drug-fastness and assessment of its degree, spectrum, duration, and other features is now in progress in Malaya, in Thailand, in Brazil, and in Africa, and cannot yet be reported. The results of these investigations will shape the future developments of chemotherapy of malaria.

Definition of Drug Resistance and its Mechanism

Each group of antimalarial drugs and also (to some degree) single compounds within a defined group have a specific effect on the malaria parasite. This effect is related to (*a*) a particular stage of the cycle of development of the plasmodium. (*b*) the species of parasite, and (*c*) the strain within a given plasmodial species. Thus all antimalarials are selective in action, and the selectivity is greatest with regard to the cycle of development of the parasite and least when it comes to the given species and strain. The response of the parasite to a drug depends not only on the biological properties of the plasmodium but also on the chemical structure, activity, and concentration of the metabolite produced in the body of the host from the administered compound.

Covell *et al.* (1955) considered resistance "only in relation to drugs which, administered to the vertebrate host in adequate and safe doses, normally destroy or contribute to the destruction of malaria parasites at some stage or other in their life-cycle."

Schnitzer and Grunberg (1957) defined drug resistance as "the temporary or permanent loss of the initial sensitivity of the micro-organism to the effect of the active substance." A more precise wording by Schnitzer (1963) does not substantially change the previous statement. Gale (1962) states that drug-resistance occurs "when an organism, previously sensitive, becomes insensitive to the drug to a degree that effectively abolishes the selective nature of the drug between the organism and its host ; resistance is therefore a fact of selective toxicity."

The new malaria terminology (W.H.O., 1963) defines drug-resistance pragmatically as "ability of a parasite strain to multiply or to survive in the presence of concentrations of a drug that normally destroy parasites of the same species or prevent their multiplication."

Each of these definitions, given advisedly in their broadest sense, is deceptively simple ; in fact, they refer to a most complex biological phenomenon. Any attempt at a more precise wording applicable to each case and able to provide a clear-cut criterion for easy recognition of resistance is virtually impossible.

The concept of susceptibility versus resistance is not a matter of a qualitative response ; it is, on the contrary, a quantitative characteristic. It is well known that the response of malaria parasites to drugs depends not only on the species of the parasite but also on the strain within the same species. Thus some strains have an inherent degree of drug tolerance and for treatment require a much higher drug dosage than other strains. Moreover, the designation of susceptibility or resistance is applied to a particular strain of the parasite, and yet our notion of "strain" is very vague and we do not know whether the absent characteristic does not exist in a larger human or plasmodial population because the sample tested is usually small and not fully representative. In fact, heterogeneity is always present because it reflects the work of natural selection on the emergence of resistant organisms.

Factors in Development of Resistance

The development of resistance in malaria parasites depends on a number of intertwined factors, among which the following are of particular importance: (1) inherent susceptibility of the plasmodium exposed to the active compound ; (2) specific

activity of the active drug or its metabolite ; (3) intensity of the infection ; (4) frequency, timing, and degree of the action of the drug ; (5) stage of the cycle of development of the parasite ; and (6) role of the vertebrate host.

1. Susceptibility of the Plasmodium

Although drug-resistance was reported in all species of malaria parasites, it seems that *P. falciparum* shows a greater variety of strains with widely different susceptibilities to the action of antimalarials, and observed cases of drug-fastness are more frequent in this parasite than in the others, though areas in which resistance has developed are limited.

2. Drug Activity

It is known to-day that the development of resistance is particularly frequent to compounds which are folic-acid antagonists (Bishop, 1959, 1962 ; J. Hill, 1963). It has been suggested that the readiness with which drug-fastness can develop is inversely related to the complexity of drug action (Rollo, 1963). Thus proguanil and pyrimethamine, though differing in chemical structure, are related to each other in their mode of action on the parasite. Both inhibit the nuclear division in the developing schizont, probably through the interference with the conversion of folic to folinic acid in the parasite-erythrocyte complex. Cross-resistance tests have shown that there is also some relationship between these two drugs and some sulphonamide compounds. Sulphonamide-fast strains are resistant to proguanil and pyrimethamine, but the converse is not always true (Bishop, 1962 ; Ramakrishnan, 1963).

The difficulty of interpreting cross-resistance in terms of biochemical relationships is equally striking in the example of human plasmodia. This was true with regard to proguanil or pyrimethamine strains of *P. falciparum* in Malaya, Tanganyika, Kenya, West Iran (Laing, 1956 ; Clyde and Shute, 1957 ; Jones, 1958 ; Meuwissen, 1961). It has now been reported from Colombia (Young, 1961), from Thailand (Young *et al.*, 1963), and independently by Powell *et al.* (1963b) from Vietnam that various strains of *P. falciparum* resistant to 4-aminoquinolines may or may not respond to pyrimethamine.

3. Intensity of Infection

It has been thought that the conditions which lead to development of drug resistance are high parasitaemia with a low concentration of active compounds. This is often found in the field when the acute attack is inadequately treated with small and irregularly spaced doses of antimalarial drugs. Bishop's (1959, 1962) studies on dynamics of incipient drug resistance in clones of *P. gallinaceum* challenged this belief.

The speed of development of resistance to proguanil was related to the number of parasites exposed to the action of the drug ; such a relationship was not evident with pyrimethamine and there was greater variability of results. Similar results using diamino-diphenyl-sulphone (D.D.S.) were obtained by Ramakrishnan *et al.* (1962) in simian malaria.

The sudden appearance of resistance to proguanil or pyrimethamine, the variation in the rate of its development, and its relative stability support the theory that drug-resistance is due to the selection of a mutant. It was thought (Bishop, 1958) that the frequency of mutation in avian plasmodia must be low, but this assumption has less validity in the case of pyrimethamine resistance of simian or human plasmodia since the resistance can be produced relatively quickly after a single dose or a few doses of the compound (Young, 1957 ; Young and Burgess, 1959 ; Burgess and Young, 1959 ; Ramakrishnan *et al.*, 1962).

4. Condition of the Drug Action

The effect of the drug dosage on the rate of development of resistance was studied on avian or simian malaria and there was no clear evidence that resistance always developed more rapidly when the dosage of pyrimethamine or proguanil was low (Bishop, 1962) ; the action of a large dosage of the drug was observed with regard to human malaria parasites by Young (1957), Young and Burgess (1959), and Burgess and Young (1959), who showed that after only two 100-mg. doses of pyrimethamine *P. malariae, P. vivax,* and *P. falciparum* developed resistance to the drug. Ramakrishnan (1963) stresses that the selection of resistant strains is rapid when a large parasite population is exposed to large drug doses with rapid sub-passages.

5. Stage of Parasite Development

Although drug-resistance must be eventually considered in relation to all developmental forms, the practical problems are generally considered in relation to blood forms only, as they play the most important part in the acute plasmodial infection.

Acquired resistance to proguanil and pyrimethamine is most easily recognized in asexual forms, but there is no doubt that it extends to gametocytes and persists through the cycle of development in the mosquito. The resistance to proguanil did not extend to secondary tissue stages in experimental avian malaria when the drug was given during the latent infection (Bishop, 1958). This is probably due to the significant differences of the metabolism of tissue forms as compared with blood forms, but the small number of tissue schizonts may also play a part. There is no evidence that resistance can be produced in human plasmodia by the action of the drug on exoerythrocytic forms.

The decrease or disappearance of drug-resistance in the absence of the drug may be due to dilution with normally sensitive parasites in areas of heavy transmission, to mutation or gradual loss of a specific adaptive mechanism, or to some possible "biological disadvantage" of resistant variants in competition with parasites of normal sensitivity.

6. Role of the Vertebrate Host

The role of the vertebrate host in the mechanism of drug resistance in plasmodia is very little known, although it should be considered from two angles: that of the biochemical characteristic of the drug metabolite acting on the parasite, and that of the immune response of the host. Chemical changes of the drug absorbed by the host are a rule in pharmacology and yet the identity and site of action of these metabolites are largely unknown and probably different in experimental animals and in man (Schmidt *et al.*, 1963 ; Gaudette *et al.*, 1961). Recent work based on the use of drugs labelled with various radioisotopes explained a few points related to the synthesis of nucleic acid by the malaria parasites (Schellenberg and Coatney, 1961), and this method seems to open new ways for the study of biochemistry of resistance in protozoa.

The role of immunity in relation to drug-resistance is little known though its importance may be considerable. Clyde (1958), observing the difference between parasite rates and parasite densities in an African community where *P. falciparum* strains resistant and susceptible to pyrimethamine existed at the same time, suggested that the immune processes are more effective against the former. On the other hand, there is evidence from the study of drug-resistance in trypanosomes that some antibody-resistant strains develop also drug-resistant characters (Soltys, 1958, 1963). This observation may or may not have a causal link, but, if confirmed, it may be of some importance in explaining the frequency of appearance of drug-resistance in highly endemic tropical areas, and especially with regard to *P. falciparum.*

Much remains to be done to increase our understanding of the biological mechanism of drug-resistance of malaria parasites. This phenomenon may be due to the phenotypic adaptation of some micro-organisms to new environment, so that growth is maintained by a gradual change of metabolic pathways, as postulated by Hinshelwood ; however, the work by Bishop (1959, 1962) indicates that drug-resistance is due mainly to a spontaneous (or induced) mutation with subsequent selection of the drug-fast strains. The fact remains that the mechanism of the appearance of drug-resistance in plasmodia has not yet been satisfactorily explained.

Future Research on Chemotherapy of Malaria

The scope of research related to the problem of drug-fastness covers three main areas: (*a*) collection of data and assessment of the distribution, degree, and other characteristics of drug resistance ; (*b*) study of the biological mechanisms involved, and (*c*) search for new compounds that could be used as alternative therapeutic agents.

The well-known difficulties of any research on drug-resistance of protozoa are particularly great in respect of malaria parasites. Observations in the field are often incomplete and seldom comparable because of the variable response of strains of plasmodial species in the human host. The important practical question arises whether there is a certain quantitative threshold of the susceptibility of any species of the malaria parasite that could be regarded as proof of drug-fastness. Since the response of the parasite depends on the inherent tolerance of the drug by the host and by the plasmodium, on the duration of exposure, and on other factors, the adoption of a definite criterion of resistance is most difficult. Nevertheless it seems that some definite parasitological and pharmacological specifications for recognition of probable drug-resistance can be agreed upon, at least for some groups of antimalarial drugs (Young and Eyles, 1963). Such a tentative agreement is now being prepared by the World Health Organization (Bruce-Chwatt, 1963).

What about the perspectives of research on biological and pharmacological aspects of drug-resistance in plasmodia ? Study of resistant strains is hampered not only by the obligatory intracellular habitat of malaria parasites but also by the fact that there is no convenient experimental animal that can be infected with human malaria. Investigations based on avian, rodent, and even simian malaria, as also results of much excellent work on drug-resistance of other blood protozoa (Bishop, 1959 ; Goodwin and Nimmo-Smith, 1962), must be interpreted with caution. The true evaluation of the characteristics of resistant strains of human plasmodia requires either a method for long-term cultivation of malaria parasites *in vitro* or the possibility of reproducing the infection, in all its stages, in a convenient experimental animal and, finally, the reliable assessment of the results on human malaria. The first two conditions have not yet been obtained ; the third is only exceptionally possible at the present time.

Where do we stand with regard to the number of good antimalarials available as alternatives in case of resistance ? With quinine having been replaced largely by synthetic compounds, most antimalarial drugs at present in general use have resulted from the intensive investigations carried out during and after the second world war. Out of at least 20,000 compounds that have been studied and screened for antimalarial activity few have survived the selection process resulting from use in the field. Of the synthetic compounds which were finally selected, less than a dozen have gained lasting importance for treatment of human malaria ; chloroquine, amodiaquine, proguanil, pyrimethamine, and primaquine or quinocide are at the present time the best antimalarials available. Do we need any more or better drugs ?

Considering the present trends and needs of chemotherapy of malaria, there is a striking difference between the approach of the clinician interested in the treatment of an individual and that of the malariologist whose aim is the eradication of this infection from a large community. The clinician has at his disposal a good range of at least five drugs for the prevention or treatment of all stages of the disease and feels no great need for new compounds ; the malariologist, dealing with a sick community, faces a problem of a different size and type. Working in highly malarious countries, usually with undeveloped public health services, he is unable to achieve his objective unless he is supplied with a drug with a faster action and longer activity than any now available. Thus socio-economic shortcomings of underdeveloped countries are a serious obstacle to making full use of our existing drugs, and to employing them more widely in malaria-eradication programmes (Bruce-Chwatt, 1956 ; W.H.O., 1961).

Need for New Antimalarials

Hence the often expressed pious wish for an " ideal antimalarial " combining the virtues of causal prophylaxis, suppression, rapid and complete curative action, sporontocidal effect, and impossibility to create resistance, together with low toxicity, prolonged action, palatability, and (last but not least) low cost. In the absence of such a wonder drug and with little hope of its imminent discovery, it is agreed that we need at the present time at least two new antimalarials with the following characteristics: (1) a potent and safe schizontocidal drug which would maintain its effect for three to six months after a single dose—it would be better still if this drug had a rapid and prolonged sporontocidal action ; and (2) a good and safe anti-relapse drug capable of effecting a radical cure of *P. vivax* and *P. malariae* when given at a single dose or at most in a three-day treatment (W.H.O., 1961).

It is not unlikely that the first of these two types of drugs is now in *statu nascendi*: it has been announced in the U.S.A. (Thompson *et al.*, 1963 ; Schmidt *et al.*, 1963 ; Coatney *et al.*, 1963) that an experimental compound known under the code name CI-501, when given in a single intramuscular injection, has continued to protect volunteers from induced malaria for several months. Bites of heavily infected mosquitos did not cause malaria in these subjects, while control subjects invariably developed the disease. It appears that the injected drug forms a " depot " from which the active compound is slowly released into the blood-stream. CI-501 is a pamoic acid salt of a dihydrotriazine which is a metabolite of proguanil. The investigators cautioned that, although CI-501 has produced spectacular results in the preliminary trials, its effect under field conditions is still to be assessed.

Much previous work on candidate antimalarial drugs did not fulfil the great expectations. A derivative of hydroxynapthalene developed in the United Kingdom had no advantage over existing compounds ; various pyrocatechol compounds and 6-aminoquinolines are being tested in Federal Germany ; Polish scientists are investigating antimalarial properties of phenylamidine ureas ; in France, in Switzerland, and in the U.S.S.R. other drugs are screened for plasmodicidal properties. However, by and large it appears that since the introduction of pyrimethamine, over ten years ago, there has been no spectacular progress in the field of malaria chemotherapy. Some " new " compounds represent improvements of already existing products rather than any salient advances. One of the reasons for this is that applied research in chemotherapy of malaria is still largely empirical.

Schulemann (1956) said that experimental chemotherapy is both a science and an art in which a sudden inspiration born out of experience gives the lead. Harington (1957), in discussing the uncertainties and lack of fundamental knowledge that bedevil experimental chemotherapy, says " the life of a chemist working in this field consists of long periods of unexciting work with occasional successes ; even these successes may be intellectually disappointing if they bear

little relation to the thought that he has put into his research." Friedheim (1959) pointed out that the apparently simple recipe of tailoring the biochemical changes produced by the drug to the differential sensitivities of the host and the parasite depends in the final account on a great deal of good luck. One is forced to admit that the knowledge of the relationship between the chemical constitution and biological activity of a compound is still poor in spite of decades of research work in laboratories of pharmaceutical industry (Goennert and Kolling, 1962). Even the Woods-Fildes approach through competitive antagonism by metabolite analogues, so successful in some cases, is largely unpredictable (Woolley, 1959).

Hawking (1963) stresses the fact that the effective chemotherapeutic compounds are usually discovered first, and only later the mechanism of their action becomes obvious. A remarkable degree of hindsight is often displayed in the course of discussions on the plasmodicidal action of antifolic acid compounds!

Successful chemotherapeutic research depends on exploiting differences between the metabolism of the infecting organism and that of the host; both these metabolisms are infinitely complex and largely unknown. Consequently most of our present remedies have been discovered by empirical methods (Hawking, 1963). Since any detailed scientific planning of a major advance in chemotherapy is difficult, the best guarantee not to miss a happy accidental discovery lies in submitting many compounds to standard screening tests. This is still the most reasonable and direct though costly and time-consuming approach (Shannon, 1948). No wonder that nearly all the advances in chemotherapy have for some decades come from large pharmaceutical companies able to use for this purpose the highly specialized skills of their research teams.

This type of research is monotonous, chancy, and expensive, whether the company is competing to fill a clear gap in the therapeutic field or simply looking for added commercial prestige. Why, then, is the number of potentially useful antimalarials resulting from such "organized opportunism" (Keele, 1962) so disappointingly low? Perhaps one of the major reasons for this meagre harvest is that until now the crying need for new antimalarials has been evident only to a small number of specialists devoted to malaria eradication.

A Long-term Commitment

The progress of global malaria eradication was until now rapid and spectacular, even though a few programmes have encountered difficulties either of a technical or an administrative kind. But malaria eradication in Africa will be a long-term commitment in which drugs will play an important part. Resistance of malaria parasites to drugs has not yet become an obstacle to the progress of malaria eradication, but the present situation may change and some forward planning is urgently needed to meet any emergency.

This was the general consensus of opinion of the recent seventh International Congress of Tropical Medicine and Malaria, held in Rio de Janeiro in September, 1963, and an appropriate resolution was passed.

The appearance of resistance of some malaria parasites to 4-aminoquinolines came as a shock and revealed the relative poverty of our chemotherapeutic arsenal and the narrow margin of safety when it comes to treatment of disease caused by plasmodia resistant to the best of our present drugs.

In planning for future research on new antimalarials, one problem must be stressed to-day, though it already has been given much thought by Findlay (1951) and by Russell (1955).

Most of the previous brilliant research on experimental chemotherapy of malaria and nearly all the recent work on drug-resistance of human plasmodia was finally assessed on induced malaria of man. The part played in this field by malaria-therapy centres in France, Great Britain, Italy, the Netherlands, Rumania, U.S.A., and U.S.S.R. tends to be forgotten. The Malaria Reference Laboratory at Horton Hospital, Epsom, observed during the past 38 years of its existence about 12,600 cases of induced malaria (Covell and Nicol, 1951; Covell, 1956; Shute, 1958). The two Rumanian centres at Berceni and Sokola recorded nearly 12,000 observations (Ciuca, 1955). With the present dearth of neurosyphilitic patients, well-planned investigations based on human malaria of non-immune subjects are virtually impossible.

Undoubtedly in some exceptional circumstances, when the safety of relevant compounds can be guaranteed, new drugs may be tried out on cases of naturally occurring malaria in tropical areas. But the response to drugs in semi-immune groups infected with unknown strains of the malaria parasite may vary considerably from one individual to another, and the only consistently reliable results can be obtained in non-immune subjects (Davey, 1963).

Experiments on Man

All the recent and reliable information on the action of new drugs and on the spectrum of resistance of malaria parasites came from careful studies carried out in the United States of America on experimental human malaria in volunteers. It has been pointed out that without such studies any future progress in chemotherapy of this disease will be uncertain and slow (W.H.O., 1961). No research of comparable value has been reported from other countries, mainly because of adverse public opinion concerning any experiments on man.

There is little doubt that the infamous "medical experiments" carried out in the concentration camps of the Third Reich and revealed in all their horror during the Nuremberg Trial (Mitscherlich and Mielke, 1962) are responsible for this attitude. Possibly some reaction may be attributed to essentially different, more recent trends connected with hospital drug trials; and the uncompromising attitude such as shown by Pappworth (1962) in his disturbing report on "human guinea-pigs" in hospitals reflects the feelings of many people and cannot be ignored. A recent editorial (*B.M.J.*, 1962) drew attention to this aspect of clinical research, and some facts concerning malaria drug trials carried out on volunteers in U.S.A. were subsequently clarified by Shannon (1963). Problems of medical ethics in controlled drug trials in hospitals were lucidly discussed by Spinks (1962) and by A. B. Hill (1963), and it is obvious that they cannot be easily solved. On the other hand, it may be argued that some current investigations carried out on hospital patients without their knowledge are legally and ethically less justifiable than the straightforward and reasonably harmless malaria research work done on healthy human volunteers with the full agreement of the subjects concerned. One can only respect the humanitarian motives of an outright rejection of the use of induced malaria in human volunteers, but the consequences of such renunciation of any major advance in the chemotherapy of a prominent disease must be fully understood and carefully considered. The issue at stake is important and the problem is difficult, but it is no good pretending that it does not exist.

The way out of this dilemma was indicated by Himsworth (1962) in his Harveian Oration. The "social contract" between the community and a special group within it is valid only if the members of that group "have standards of integrity both personal and intellectual more exacting than that expected of the community in general . . .; and only in so far as society concedes authority to our judgment in matters

that fall within our competence . . . can we render the service required of us."

Irrespective of the methods used now or in the future there is no doubt that the progress in chemotherapy of malaria must be encouraged and assisted as much as possible, and it is to be hoped that the applied research in this field, spurred on by the "sweet uses of adversity" and based on more fundamental knowledge, will become more rational and more productive.

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